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OFFICIAL

Date December 13, 2002

To Jennifer Kim
U.S. Patent and Trademark Office (Patent)
Assistant Commissioner for Patents
Washington, DC 20231
Telephone:

Facsimile number 06275-15000003 / 703 308 4556

From Celia H. Leber

Re New Use For Budesonide and Formoterol
Your Ref.: D 1841-3P US
Our Ref.: 06275-150003

Number of pages including this page 13

Message

Attorney's Docket No.: 06275-150003 / D 1841-3P US

#12
m.m.
1/9/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer et al. Art Unit : 1617
Serial No. : 10/010,283 Examiner : Jennifer Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF DECLARATION OF CHRISTER HULTQUIST, M.D.

In response to the action mailed July 30, 2002, and further to Applicants' response filed December 2, 2002, Applicants submit the following remarks and attached Declaration.

REMARKS

Supplemental to the response filed on December 2, 2002, Applicants submit the attached Declaration of Christer Hultquist, M.D. In this declaration, Dr. Hultquist discusses the data that was introduced in Applicants' response. As explained in the Declaration, Dr. Hultquist was involved in conducting the trial that generated this data.

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

December 13, 2002
Date of Transmission

Julia Doherty
Signature

Julia Doherty
Typed or Printed Name of Person Signing Certificate

Applicants ask that all claims be allowed. It is believed that no fee is required by this submission. However, if any fee is due, Applicants authorize withdrawal of the fee from Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: December 13 2002

Reg No 30,125

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Attorney's Docket No.: 06275-150003 / D 1841-3P US

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BOX AF
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF CHRISTER HULTQUIST, M.D.

I, Christer Hultquist, M.D., declare as follows:

1. I am a physician with a Specialty in Pediatrics (1981) and in Pediatric Allergology (1982). From 1981 to 1991 I was Senior Registrar at the Pediatric unit at the University Hospital in Lund, Sweden, attending children with cystic fibrosis, asthma and related allergic disorders. Since 1991 I have been a Medical Advisor at Astra AB (now AstraZeneca AB), and at present I am serving as the Clinical Development Medical Director for Symbicort® asthma medication (an inhalable medication containing a combination of budesonide and formoterol) at AstraZeneca AB.

2. I was involved in conducting a placebo-controlled 12 month clinical trial that was recently performed using a combination of budesonide/formoterol (under the product name Symbicort®) in the treatment of moderate to severe COPD. 1022 patients were treated in a 2 week initial period with oral prednisolone (30 mg once daily) and formoterol (2 x 4.5 µg twice daily). The patients had the following profile:

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

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Age ≥ 40 years

COPD patient for at least 2 years

At least 10 pack years smoking history[1]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/formoterol combination (Symbicort® inhaler) at a dosage of 2 puffs, each puff containing 160 µg budesonide/4.5 µg formoterol, twice per day

Group 2: Budesonide alone (2 puffs, each containing 200 µg budesonide (metered dose, equivalent to the 160 µg dose in the Symbicort® inhaler), twice daily)

Group 3: Formoterol alone (2 puffs, each containing 4.5 µg formoterol, twice daily)

Group 4: Inhaled a placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded.

3. The results of this study showed a synergistic effect from the combination of budesonide and formoterol.

For example, as shown in the graph titled "Symbicort Reduces No. of Severe Exacerbations/Patient/Year"[2] (Appendix 1, submitted herewith), as compared to the placebo (Group 4), treatment with formoterol alone (Group 3) increased the number of exacerbations slightly (+3%), and treatment with budesonide alone (Group 2) decreased the number of exacerbations by 12%. Thus, it would be expected that the additive effect of the

[1] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

[2] Severe exacerbations were considered to be exacerbations requiring medical intervention, i.e., administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

budesonide/formoterol combination would be a 9% reduction in exacerbations. Instead, Group 1, treated with the budesonide/formoterol combination, exhibited a 24% reduction in exacerbations.

4. A synergistic effect was also observed in the morning peak expiratory volume (PEF) of the patients, as shown in the graph titled "Symbicort Improves Morning PEF" (Appendix 2, submitted herewith). The difference in adjusted mean change of morning PEF, as compared to the placebo, was 3.5 L/min for the patients treated with budesonide alone, 11.1 L/min for those treated with formoterol alone ($p<0.001$), and 18.3 L/min for the patients treated with the budesonide/formoterol combination, i.e., 3.7 L/min higher than the additive result that would have been expected.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

By: C. Christer Hultquist Date: 2002-12-06

Christer Hultquist, M.D.

CURRICULUM VITAE

Name
Christer Hultquist

Date of birth
1 October 1946

Nationality
Swedish

Education
1977 fully qualified physician

Postgraduate training
1981 Certified. Pediatrician
1982 Certified in Pediatric Allergology

Professional appointements
Member of the Staff and Senior Registrar, Department of Pediatrics, University of Lund, 1981-1991.
Medical Adviser, Astra Draco AB, Lund, 1991-99.
AstraZeneca 1999-2000
- Global Product Physician, Pulmicort, 1999-2000
- Global Product Physician, Symbicort, June 2000 –Feb 2002
- Clinical Development Medical Director, Symbicort, March 2002

Professional associations
Swedish Pediatric Association
Swedish Pediatric Association for Allergy and Immunology
Swedish Association for Pulmonary Medicine
Swedish Association for Allergology
ERS
ATS

Lund 13 September 2002

Christer Hultquist

Publications

1. Wettrell G, Hallböök T, Hultquist C. Reflex Sympathetic Dystrophy in Two Young Females. Acta Ped Scand 1977;68:923-4.
2. Hultquist C, Kjellman B. Pricktestning på barn. Läkartidningen 1980;77:1213-4, 1217.
3. Hagqvist G-R, Hultquist C, Kjellman, B. Pricktestning på vuxna. Läkartidningen 1980;77:1215-7.
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5. Hultquist C, Lindberg C, Nyberg L, Kjellman B, Wettrell G. Kinetics of terbutaline in asthmatic children. Eur J Respir Dis 1984;65, Suppl. 134:195-203.
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7. Hultquist C, Lindberg C, Nyberg L, Kjellman B, Wettrell G. Pharmacokinetics of Intravenous Terbutaline in Asthmatic Children. Dev Pharmacol Ther 1989;459:1-6.
8. Hultquist C, Ahlström H, Kjellman N-I, Malmqvist L-Å, Svenonius E, Melin S. A double-blind comparison between a new multidose powder inhaler (Turbuhaler) and metered dose inhaler in children with asthma. Allergy 1989;44:896-9.
9. Hultquist C. Nebulized Budesonide in Severe Childhood Asthma. Lancet 1989;i:380.
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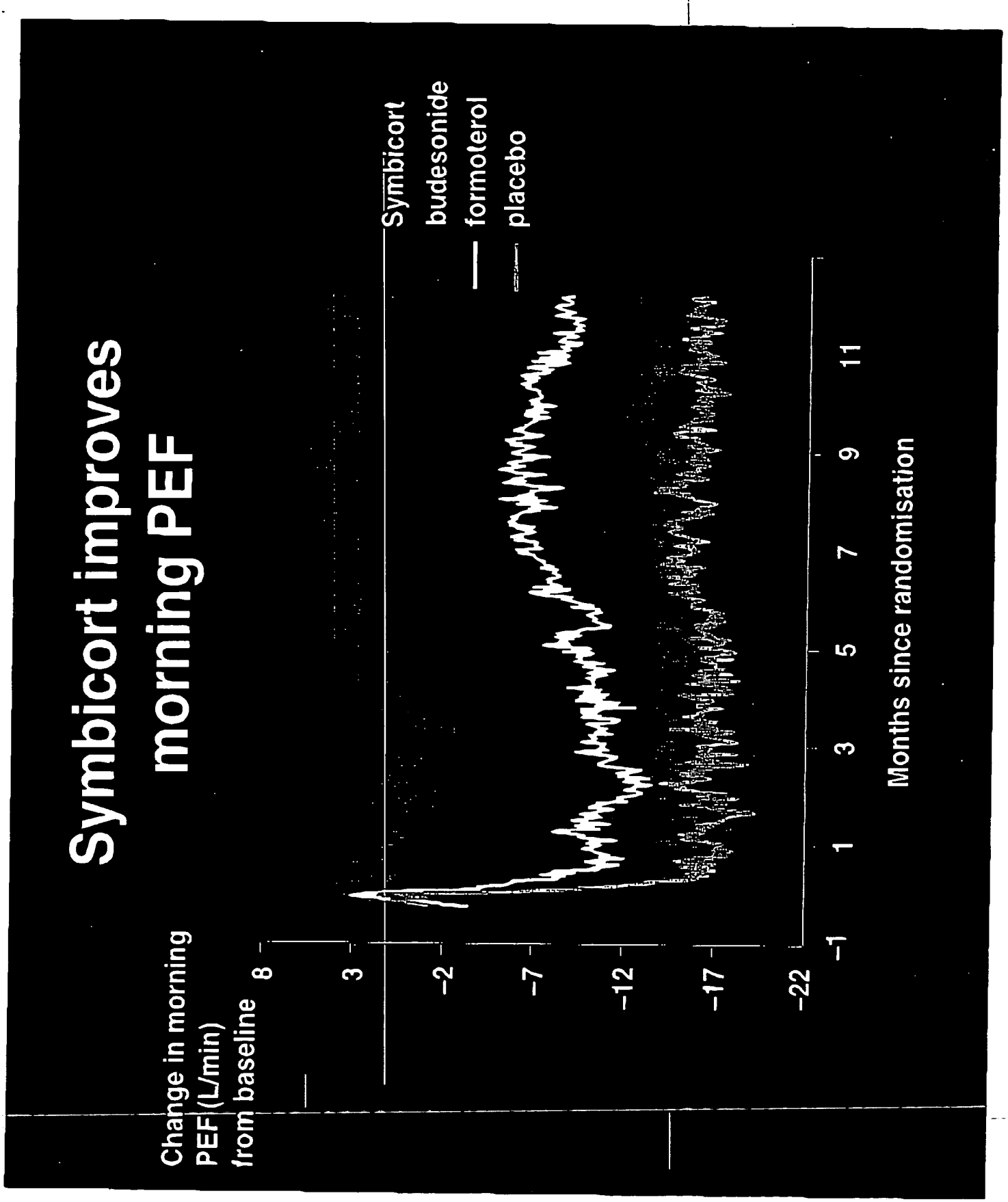
11. Hultquist C, Wollmer T, Eklund G, Jonson B. Effect of inhaled terbutaline sulphate in relation to its deposition in the lungs. Pulmonary Pharmacology 1992;5:127-32.
12. Oxelius V-A, Hultquist C, Husby S. Gm allotypes as indicators of non-atopic and atopic bronchial asthma. Int Arch Allergy Immunol 1993;101:66-71

13. Jonasson G, Carlsen K-H, Hultquist C. Low dose budesonide improves exercise induced asthma in schoolchildren. Pediatr Allergy Immunol 2000;11:120-25.

14. Hultquist C. Sociala förmåner och rättigheter. Ett kapitel i Barnallergisektionens bok "Astma och allergi hos barn"

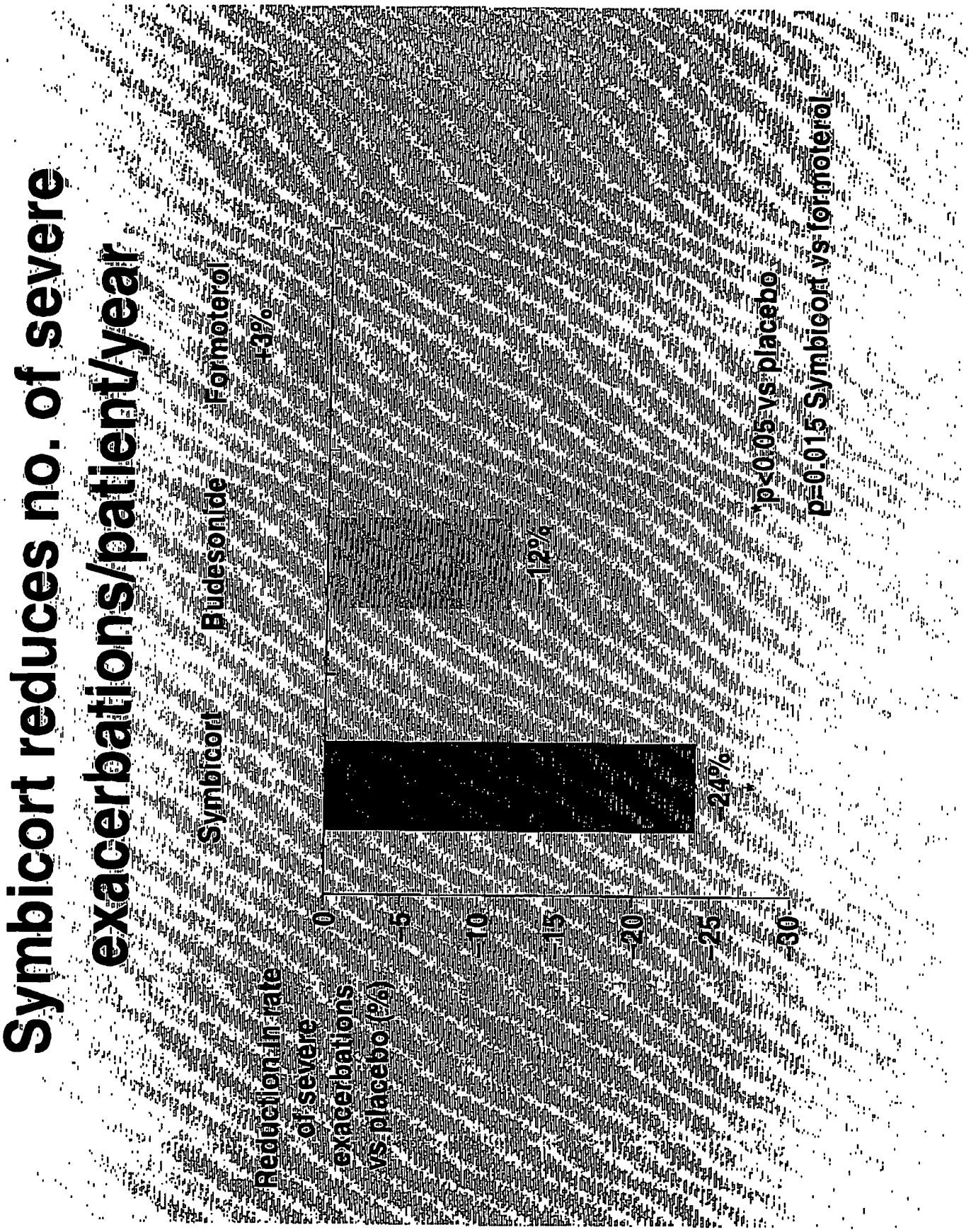
Lund 13 September 2002

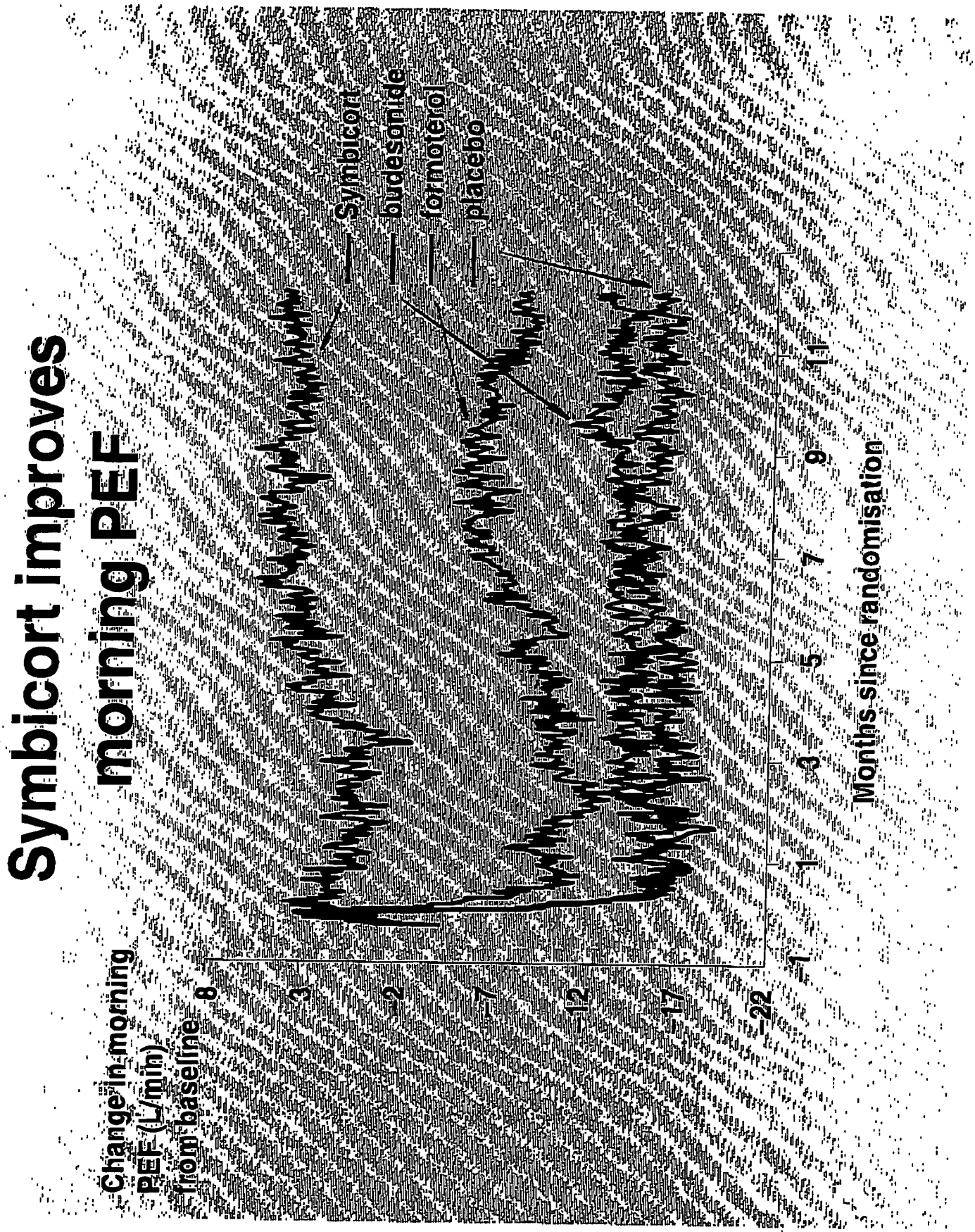
Christer Hultquist



Symbicort reduces no. of severe exacerbations/patient/year

Symbicort reduces no. of severe exacerbations/patient/year





Julia Doherty

From: Celia Leber
Sent: Friday, December 13, 2002 10:30 AM
To: Julia Doherty
Subject: 06275-150003 (New Use For Budesonide and Formoterol)

Here is the transmittal to fax with the Declaration of Christer Hultquist for the above case (the one you faxed me on Weds.). Please have Janis sign, if she is available, otherwise Tim French. Please file this today by fax, and let me know when it is all set. Thanks!!

Transmittal enclosing declarat...

Transmittal enclosing declaration of Dr. Hultquist